REMARKS/ARGUMENTS

Claims 1-9 and 11-21 are pending in the application. Claim 16 is amended herein. No new matter has been introduced by way of this amendment.

I. Claims 1, 2, 4-6, 8, and 9 are patentable over U.S. Patent No. 6,506,894 to Barany *et al.*

The rejection of claims 1, 2, 4-6, 8, and 9 under 35 U.S.C. § 102(e) for alleged anticipation by U.S. Patent No. 6,506,894 to Barany *et al.* ("the Barany patent") has been maintained. Applicants respectfully traverse the rejection.

Claim 1 recites methods of preparing a polynucleotide having a target sequence from a plurality of oligonucleotides by coupling oligonucleotides to form a plurality of coupled oligonucleotides, each of which represents a region of sequence of the polynucleotide and *shares at least one terminal region of sequence with at least one other* ***coupled*** *oligonucleotide* and assembling the polynucleotide by extension of the coupled oligonucleotides. Claims 2, 4-6, 8, and 9 depend from claim 1.

U.S. Patent No. 6,506,594 to Barany *et al.* ("the Barany patent") describes a ligase detection reaction for identifying nucleic acid sequence differences. The methods of the Barany patent include a ligation phase, a capture phase, and a detection phase. In the ligation phase, a first oligonucleotide probe having a target-specific sequence and an "addressable array-specific" portion and a second oligonucleotide probe having a target-specific sequence and a detectable reporter label are hybridized to the target sequence. When the two probes hybridize to the target sequence adjacent to one another and no interfering mismatch is present, ligation of the probes occurs in the presence of a ligase. The capture phase involves hybridization of the addressable array-specific portion of the first probe to a complementary capture oligonucleotide bound to solid support. Detection of the presence of the reporter label on the solid support indicates the presence of a sequence in the sample (the Barany patent at column 10, line 14 to column 11, line 7).

The Barany patent, however, does not teach, either expressly or inherently, generation of a coupled oligonucleotide sharing at least one terminal region of sequence with at least one other coupled oligonucleotide. Applicants respectfully submit that the Examiner has

misunderstood the meaning of the phrase "shares at least one terminal region of sequence with at least one other coupled oligonucleotide." A shared terminal region of sequence refers to a region of the nucleotide sequence of *coupled* oligonucleotide #1 that also is present in *coupled* oligonucleotide #2, not that the ends of the oligonucleotides to be joined are shared upon coupling by virtue of, for example, ligation, or that the nucleotide sequence of the ends of the coupled oligonucleotides are complementary. For example, coupled oligonucleotide #1 comprising G1-G2 and coupled oligonucleotide G2-G3 share a terminal region of sequence, G2 (see specification, for example, at Figures 1 and 2). Applicants respectfully submit that the definition of the term "coupling" in the specification as the covalent joining of two molecules is irrelevant. As the Barany patent fails to teach coupled oligonucleotides having at least one shared region of terminal sequence with another coupled oligonucleotide, the Barany patent cannot anticipate claims 1, 2, 4-6, 8, and 9.

The Barany patent also does not teach extension of coupled oligonucleotides by overlap PCR as set forth in claim 9. The shared terminal region of sequence between coupled oligonucleotides allows for extension of the oligonucleotides by this method (see specification, for example, at Figures 1 and 2). For this additional reason, claim 9 is novel over the Barany patent.

Claim 6 adds the step of amplifying *coupled* oligonucleotides prior to assembly of the polynucleotide. In other words, the amplification occurs *after* the ligation step. In contrast, the Barany patent describes amplification of the ***target polynucleotide sequence*** prior to the overall ligation detection reaction for the purpose of increasing the quantity of target nucleotide sequence in the sample (the Barany patent, column 14, lines 13 to 62 and Figure 3). For this additional reason, claim 6 is novel over the Barany patent.

As the Barany patent does not teach each limitation of rejected claims 1, 2, 4-6, 8, and 9, that reference cannot anticipate the present invention as defined by those claims. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 1, 2, 4-6, 8, and 9 over the Barany patent.

II. Claims 1, 2, 4, and 5 are patentable over U.S. Patent No. 6,495,318 to Harney.

Claims 1, 2, 4, and 5 are rejected under 35 U.S.C. § 102(e) for alleged lack of novelty over U.S. Patent No. 6,495,318 to Harney ("the Harney patent"). Applicants disagree.

The Harney patent describes methods of preparing multicomponent nucleic acid constructs using hybridization of complementary sequences. Like the Barany patent, the Harney patent does not teach, either expressly or inherently, a coupled oligonucleotide that shares at least one terminal region of sequence with at least one other coupled oligonucleotide. "Coupling" of oligonucleotides to generate a covalently joined coupled oligonucleotide is not the same as a shared terminal region of sequence between two coupled oligonucleotides as presently claimed. A "shared terminal region of sequence" indicates that a region of the nucleotide sequence of coupled oligonucleotide #1 also is present in coupled oligonucleotide #2, as exemplified in Figures 1 and 2 of the specification. As the Harney patent fails to teach coupled oligonucleotides having at least one shared terminal region of sequence, that reference cannot anticipate claims 1, 2, 4, and 5. Reconsideration and withdrawal of the rejection is requested.

III. Claims 1, 4, 5, 7, 8, and 11-15 are patentable over U.S. Patent No. 6,489,466 to Huang *et al.*

Claims 1, 4, 5, 7, 8, and 11-15 remain rejected over U.S. Patent No. 6,489,466 to Huang *et al.* ("the Huang patent") for alleged lack of novelty. Applicants traverse.

The Huang patent describes a method of oligonucleotide synthesis involving a cycle of deprotection, activation, and coupling steps (Huang patent, column 2, lines 17-35). The method involves addition of monomeric nucleotides and "is equivalent to natural or biological DNA synthesis, i.e., a C-5' oxygen of a monomeric nucleotide links to the C-3' phosphoramidite activated group." (Huang patent, column 10, lines 49-61.) The Huang patent fails to teach, either expressly or inherently, coupling of oligonucleotides. Moreover, the Huang patent fails to teach the synthesis of coupled oligonucleotides sharing at least one terminal region of sequence with at least one other coupled oligonucleotide, as presently claimed and explained above.

As the Huang patent fails to teach each limitation of the present claims, Applicants respectfully submit that the reference does not anticipate claims 1, 4, 5, 7, 8, and 11-15 and, accordingly, request reconsideration and withdrawal of the rejection.

IV. Claims 1-5, 7-9, and 11-19 are patentable over U.S Patent No. 6,479,262 to Delagrave.

Claims 1-5, 7-9, and 11-19 are rejected over U.S. Patent No. 6,479,262 to Delagrave ("the Delagrave patent"). Applicants disagree with the rejection.

There is no teaching by the Delagrave patent, either expressly or inherently, that the coupled oligonucleotide resulting from the coupling step shares at least one terminal region of sequence with at least one other coupled oligonucleotide. That the specification defines "coupling" as the covalent joining of two molecules is irrelevant. A shared terminal region of sequence as used in the claims refers to a region of the nucleotide sequence of coupled oligonucleotide #1 that also is present in coupled oligonucleotide #2, not that the ends of the oligonucleotides to be joined are shared upon coupling or that the nucleotide sequence of the coupled oligonucleotide ends are complementary. For example, coupled oligonucleotide #1 comprising G1-G2 and coupled oligonucleotide G2-G3 share a terminal region of sequence, G2 (see specification, for example, at Figures 1 and 2). The Delagrave patent also fails to teach extension of coupled nucleotides by overlap PCR. Accordingly, the Delagrave patent cannot anticipate claims 1-5, 7-9, and 11-19. Reconsideration and withdrawal of the rejection are requested.

V. Claims 1-6, 8, and 9 are patentable over the Barany patent in view of Walker *et al.* (*PNAS*, 72(1):122-126 (1975)).

Claims 1-6 and 8-9 are rejected under 35 U.S.C. § 103 for alleged obviousness over Barany in view of Walker *et al.* (*PNAS*, 1975, 72(1):122-126) (Walker). Applicants disagree with the rejection.

As previously noted, the Barany patent simply describes a method of detection of a target polynucleotide sequence. The Barany patent does not teach or suggest synthesis of coupled oligonucleotides sharing at least one terminal region of sequence with at least one other coupled oligonucleotide. "Coupling" of oligonucleotides to generate a covalently

linked oligonucleotide is not the same as a shared terminal region of sequence between two coupled oligonucleotides, which indicates that a region of the nucleotide sequence of coupled oligonucleotide #1 also is present in coupled oligonucleotide #2, as exemplified in Figures 1 and 2 of the specification.

The Barany patent also does not teach or suggest extension of the coupled oligonucleotides by overlap PCR as set forth in claim 9. The shared terminal region of sequence between coupled oligonucleotides allows for extension of the oligonucleotides by this method (see specification, for example, at Figures 1 and 2).

The Walker reference fails to remedy the deficiencies of the Barany disclosure. Walker makes no mention of terminal regions of shared sequence or extension of the coupled oligonucleotides by, for example, overlap PCR, to yield the target polynucleotide.

Applicants respectfully submit that the rejection of claims 1-6, 8, and 9 over the Barany and Walker references is improper, as the cited references fail to teach or suggest each limitation of the present claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

VI. Claims 1 and 4-9 are patentable over the Huang patent in view of the Harney patent.

Claims 1 and 4-9 are rejected for alleged obviousness over the Huang patent in view of the Harney patent. Applicants traverse.

Neither the Harney patent nor the Huang patent teaches or suggests synthesis of a coupled oligonucleotide resulting from a coupling step that shares at least one terminal region of sequence with at least one other coupled oligonucleotide. "Coupling" of oligonucleotides to generate a covalently joined coupled oligonucleotide is not the same as a shared terminal region of sequence between two coupled oligonucleotides, which indicates that a region of the nucleotide sequence of coupled oligonucleotide #1 also is present in coupled oligonucleotide #2. Additionally, neither patent teaches or suggests extension by overlap PCR. Accordingly, the references fail to teach each limitation of claims 1 and 4-9 and do not render those claims unpatentable.

Moreover, the Harney patent describes methods of preparing multicomponent nucleic acid constructs using hybridization of complementary sequences. In contrast, the Huang

patent describes a method for oligonucleotide synthesis involving a cycle of deprotection, activation, and coupling steps (Huang patent, column 2, lines 17-35). Unlike the Harney method, the Huang method involves addition of monomeric nucleotides and "is equivalent to natural or biological DNA synthesis, i.e., a C-5' oxygen of a monomeric nucleotide links to the C-3' phosphoramidite activated group." (Huang patent, column 10, lines 49-61.) The Huang patent fails to teach, either expressly or inherently, coupling of oligonucleotides. Thus, the skilled artisan would not have been motivated to combine the disclosure of the Huang patent as it relates to nucleotide-by-nucleotide oligonucleotide synthesis with the methods of synthesis of multicomponent nucleic acid constructs from oligonucleotides of the Harney patent.

Applicants respectfully submit that a *prima facie* case of obviousness of claims 1 and 4-9 has not been established on the basis of the Huang patent in view of the Harney patent. Reconsideration and withdrawal of the rejection is respectfully requested.

VII. The double patenting rejection of claims 1-5, 7, 8, 11-15, 17, and 18 over claims of the Delagrave patent is improper.

Claims 1-5, 7, 8, 11-15, 17, and 18 are rejected for alleged obviousness-type double patenting in view of claims 1, 7, 10, 12, 14, 18, 20, 21, and 24-26 of the Delagrave patent. Applicants disagree.

In determining whether a nonstatutory basis exists for a double patenting rejection, the issue is whether any claim in the application defines an invention that is merely an obvious variation of an invention claimed in a patent. (MPEP § 804 II.B.1.)

The methods of the Delagrave patent relate to synthesis of polynucleotides by sequential ligation of oligonucleotide segments (the Delagrave patent at Figures 1 and 2.) The Delagrave patent, however, does not teach or suggest that the coupled oligonucleotides share at least one terminal region of sequence with at least one other coupled oligonucleotide. This element of present claims 1-5, 7, 8, 11-15, 17, and 18 is more than a mere obvious variation over claims 1, 7, 10, 12, 14, 18, 20, 21, and 24-26 of the Delagrave patent. As shown in Figures 1 and 2 of the present specification, the shared regions of terminal sequence of coupled oligonucleotides are regions of identical sequence. For example, coupled oligonucleotide #1 comprising G1-G2 and coupled oligonucleotide G2-G3 share a terminal

region of sequence, G2. The regions of shared sequence allow extension of the coupled oligonucleotides, for example, by overlap PCR, to generate the target polynucleotide sequence. The recited claims of the Delagrave patent do not teach or suggest coupled oligonucleotides sharing at least one region of terminal sequence with another coupled oligonucleotide. As such, present claims 1-5, 7, 8, 11-15, 17, and 18 are patentably distinct over the recited claims of the Delagrave patent.

Applicants respectfully request reconsideration and withdrawal of the rejection.

VIII. Claims 1 and 11-21 are patentable over the Delagrave patent in view of the Barany patent.

Claims 1 and 11-21 are rejected for alleged obviousness over the Delagrave patent in view of the Barany patent. Applicants traverse.

The Delagrave patent is not available as prior art under 35U.S.C. § 103 by virtue of section 103(c):

> Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

As the present application and the Delagrave patent are commonly owned by Hercules Incorporated, the Delagrave patent cannot be cited against the present application under 35 U.S.C. § 103. Withdrawal of the rejection of claims 1 and 11-21 over the Delagrave patent in view of the Barany patent is respectfully requested.

IX. Claim 16 as amended satisfies the second paragraph of 35 U.S.C. § 112.

Claim 16 is rejected under 35 U.S.C. § 112, second paragraph for alleged indefiniteness in recitation of the term "ddUTP-biotin." Applicants disagree with the rejection as one of ordinary skill in the art would understand the metes and bounds of the term. Nonetheless, Applicants have amended claim 16 to recite biotin-dideoxyuridine triphosphate. Accordingly, Applicants request withdrawal of the rejection.

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CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, the undersigned may be contacted at 215-557-5908.

Respectfully submitted,

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